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Review

Progression of frailty as measured by a cumulative deficit index: A systematic review

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ABSTRACT

Background: Frailty is a risk factor for adverse health outcomes. There is a paucity of literature on frailty progression defined by a cumulative deficit model among community dwelling older people. The objective of this review was to synthesise evidence on these changes in health and mortality among community-dwelling older people.

Methods: Six databases (Medline, Embase, CINAHL, Cochrane, PsycInfo, Web of Science) and a clinical trials registry were searched in July 2021. The inclusion criteria were studies using a frailty index and providing information on transition between frailty states or to death in community-dwelling older people aged $\geq$ 50. Exclusion criteria were studies examining specific health conditions, conference abstracts and non-English studies. To standardise the follow-up period and facilitate comparison, we converted the transition probabilities to annual transition rates.

Results: Two reviewers independently screened 5078 studies and 61 studies were included for analysis. Of these, only three used the same frailty state cut-points to facilitate cross-cohort comparison. This review found that frailty tends to increase with time, people who are frail at baseline have greater likelihood to progress in frailty and die, and the main factor that accelerates frailty progression is age. Other risk factors for progression are having chronic disease, smoking, obesity, low-income or/and low-education levels. A frailty index is an accurate predictor of adverse outcomes and death.

Discussion: This systematic review demonstrated that worsening in frailty was a common frailty transition, and older people who are frail at baseline are more likely to die. A frailty index has significant power to predict adverse health outcomes. It is a useful tool for within-cohort comparison but there are challenges comparing different cohorts due to dependence of frailty progression on age and differences in how frailty index is defined and measured.

1. Introduction

Ageing is associated with increased probability of ill health (Clegg et al., 2013), poor quality of life (Nikolova et al., 2020), hospitalisation (Kojima, 2016) and death (Shamliyan et al., 2013; Chang and Lin, 2015; Kojima et al., 2018). Individuals of the same age can differ greatly in terms of their underlying health (Mitnitski and Rockwood, 2015) and associated vulnerability to adverse outcomes. This variability in vulnerability is often referred to as frailty (Clegg et al., 2013). There are two established models of frailty: the phenotype model and cumulative deficit model. The phenotype model of frailty is based on the five physical characteristics as reported in the original Cardiovascular Health Study (slow walking speed, weight loss, exhaustion, weak grip strength, low energy expenditure). These physical components enable categorisation into three states: non-frail, pre-frail or frail (Fried et al., 2001). Evidence on transitions between states of the phenotype model and death has been recently summarised (Kojima et al., 2019). The cumulative deficit model counts the number of health deficits, including cognition, mood and social support (Mitnitski et al., 2001). Owing to this more comprehensive information on health, the cumulative deficit

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model is considered more sensitive to modifications in underlying health than the phenotype frailty (Cesari et al., 2014), and a more accurate predictor of mortality (Kojima et al., 2018). Thus, the cumulative frailty model may be a more useful tool to explore changes in health (Mitnitski and Rockwood, 2015) in response to interventions to improve frailty-related outcomes (Cesari et al., 2014).

A frailty index (FI) is calculated by dividing the number of present health deficits by the total number of deficits measured. The FI can take value from 0.0 to 1.0, where a higher score is associated, on average, with higher frailty. This continuous variable is useful when frailty is assessed at the individual level. To operationalise the frailty index for clinical use, it is usually categorised into a small number of ordered states based on established cut-points (Hoover et al., 2013). A set of standard criteria which include counting only deficits associated with health status, have increasing prevalence with age and cover a range of physiological systems is available to guide operationalisation of the frailty index (Searle et al., 2008). This suggests that frailty indices implemented in different samples can be based on different deficits when exploring changes in health. There is however a paucity of literature on progression in frailty defined by FI among community-dwelling older people.

The aim of this review is to synthesise the evidence on changes in health and mortality when changes are operationalised as transitions between states of a cumulative frailty model. We sought to explore whether changes could be summarised, to what extent these changes depend on baseline health and age and how often improvement occurred relative to deterioration.

2. Method

2.1. Protocol

A review protocol was developed in accordance with the Preferred Reporting Items for Systematic review (PRISMA) statement (Moher et al., 2015) (PROSPERO registration number CRD42020218187).

2.2. Search Strategy

In June 2020 we conducted searches to determine the rate of progression of frailty for groups defined by risk factors using the search strategy and search terms published in the review by Kojima et al. (Kojima et al., 2019). The search terms included database subject headings (eg MeSH) and textwords: Frail elderly (MesH), Frailty(MeSH), frailty, transition, progression, prognosis or course. These searches were rerun in full on 13th July 2021 using the same strategies and date limits in Medline, Embase, PsycInfo, CINAHL, Cochrane CENTRAL, and Web of Science and We also searched. We also searched ClinicalTrials.gov (U.S. NIH) to identify any ongoing trials. Since the frailty index was introduced in 2001 (Mitnitski et al., 2001) we limited our search to articles published from 2000. The search strategies were peer reviewed by an information specialist using the PRESS checklist (Mcgowan et al., 2016). Please see Supplementary 1 for full search strategies.

The results of the database searches were stored and de-duplicated in an EndNote X9 library. Further relevant studies were sought by citation searching (backwards) of the included studies.

2.3. Study selection

As opposed to Kojima et al. (2019) review where they synthesised evidence of transitions between frailty states with phenotypic frailty defined by Fried et al. (2001) we limited our search to articles where frailty is defined by a frailty index defined by Mitnitski et al. (2001).

Screening was conducted in two stages using the Rayyan web tool (Ouzzani et al., 2016). Two authors (DK, HJ) independently screened titles and abstracts for eligibility followed by reading of the full texts. Disagreements were resolved with a third reviewer (SN). We included studies which: 1) used a frailty index defined by Mitnitski et al. (2001); or used both approaches; 2) studied people aged 50 and over living in the community, as nationally representative cohorts of respondents in different countries focus on individuals aged 50 and over (Mansor et al., 2019; Perianayagam et al., 2019; Shin, 2019; Ichimura et al., 2009; Zaninotto and Steptoe, 2019; Börsch-Supan et al., 2013; Rosero-Bixby et al., 2019; Wong et al., 2015, Kearney et al., 2011, Sonnega et al., 2014, Zhao et al., 2012); 3) provided information on transition between frailty states or to death; 4) published since 2000; and 5) prospective design. We excluded studies which: 1) used only phenotypic frailty defined by Fried et al. (2001); 2) analysed only a selected sample (e.g., people with specific health conditions); 3) conference abstracts and reviews; 4) non-English studies.

2.4. Quality assessment

The quality of the included studies was assessed using a modified Newcastle-Ottawa scale (NOS) (Wells et al., 2000). We modified NOS to include an additional criterion – the frailty index must include at least 30 deficits as suggested by Searle et al. (2008).

2.5. Data extraction

Data were independently extracted by two reviewers using an Excel spreadsheet. Data extracted directly from the studies included: first author's name, publication year, cohort name, sample size, mean age at baseline, proportion of female participants, cohort characteristics, duration of follow up, follow up rate, cut-points for FI score, number of deficits used to construct FI, number and percentage of participants in each frailty category (non-frail, pre-frail, frail) at baseline and follow up as well as number and percentage of deaths at follow up.

2.6. Data synthesis

Due to the heterogeneous nature of many frailty studies, we synthesised evidence from studies which used the same cut-points. Data on changes of frailty status from baseline to follow up were converted to annual transition probabilities by calculating the *N*th root of a transition probability matrix using eigen-decomposition approach introduced in Chhatwal et al. (2016). Unlike the traditional method the eigen-decomposition method matches exactly the observed probabilities for lower frequencies. The findings from the rest of the studies were narratively synthesised to investigate associations between socio-demographic factors and progression in frailty.

3. Results

3.1. Selection processes, study characteristics and assessment of study quality

The final search identified a total of 10697 records. After deduplication 5619 articles were screened. Of these, 4977 studies were excluded through title and abstract screening. The full texts for one hundred and one studies were reviewed of which fifty-seven were excluded because they used a selected sample (n = 7), used a frailty definition which did not meet the cumulative frailty model criteria or did not contain information on changes between frailty categories and/or death (n = 26). We also excluded systematic reviews (n = 1), non-English publications (n = 1), and conference abstracts (n = 21). The full text for one study was not found. Sixty one studies were identified for inclusion in the current systematic reviews. The PRISMA flow diagram is presented in Fig. 1. Citation searches identified sixteen records. The detailed study characteristics of included studies are presented in Table 1.

The majority of included studies reported data extracted from longitudinal population-based cohort studies and local administrative data

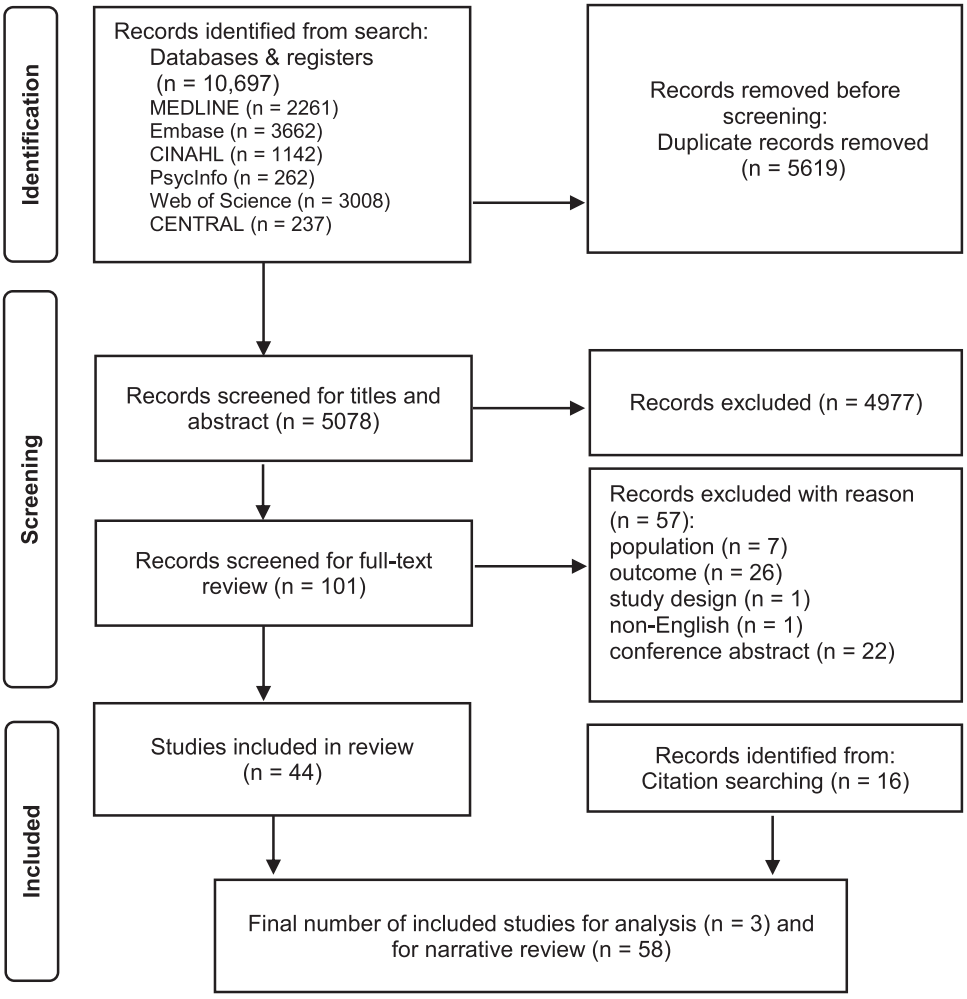

Fig. 1. PRISMA flow diagram.

spanning more than eighteen countries: United States (n = 8), Canada (n = 9), England (n = 8), China (n = 7), the Netherlands (n = 4), Australia (n = 2), France (n = 2), Germany (n = 2), Korea (n = 2), Wales (n = 1), Great Britain (n = 1), Sweden (n = 1), Spain (n = 1), Turkey (n = 1), Japan (n = 1), Taiwan (n = 1), Brazil (n = 1), Mexico (n = 1). Most measured FI in accordance with the Searle et al. (Searle et al., 2008) guidance, and one study (Jung et al., 2014) proposed a novel approach to create FI, which applies weighting factors with respect to clinical significance.

Only three of the sixty-one included studies (Fig. 1) used more than 30 deficits to calculate FI score and discretise it into three categories: non-frail, pre-frail and frail. The cohorts were from Australia (n = 1), and China (n = 2), their participants' mean age at baseline varied between 70 and 80 years, all consisted of more women than men. These three studies were related to be of good quality (the NOS score is 9, Supplementary Table 3). The remaining fifty-eight studies used different number of deficits used as well as cut-points. Information reported in the remaining fifty-eight studies was used for a narrative summary.

3.2. Annual transitions between frailty states and to death

Table 2 presents annual transition probabilities extracted from the three included studies (ID:1,2,3). As cycle length was respectively 4.5, 2, and 3 years we converted to annual transition probabilities using an eigen-decomposition technique (Chhatwal et al., 2016). Findings suggest participants were likely to remain in their current frailty category (non-frail state 86%, 84%, 62%; pre-frail state 79%, 57%, 70%; and frail state 89%, 68%, 65%). Most transition in either direction are gradual. Results from the three cohorts highlight the decline in health with annual transitions from pre-frail to frail status being 13%, 15%, 15%. Frail participants at baseline were more likely to die in all three studies.

Health tends to decline with age. In support of this observation, we have found that age tends to accelerate transition from being non-frail to frail (34% vs 13%) and from being frail to death (28% vs 12%) when comparing youngest (mean age 69.4 (ID:2)) to oldest (mean age 82.6 (ID:3)) cohort. At the same time the youngest cohort had almost 30% chances of health improvement by going from pre-frail to non-frail state.

3.3. Narrative synthesis

Fifty-eight studies did not report sufficient data for analysis but provided additional information to describe the complex nature of these changes. Many of them reported that frailty tends to increase over time (ID:5,8,9,12–14,27,36,38,39,49,52,54), and greater frailty at baseline increased the likelihood of increasing frailty at follow ups (ID:12,17,21,22,44). One study which measured frailty transition times using the electronic FI (Clegg et al., 2016) reported that the frailty transition times shorten as a frailty state deteriorates (ID:52). Other studies reported that improvement in frailty is also possible (ID:9,12,13, 36,57,46).

3.4. Association between FI, age and gender

Whilst the included studies consistently reported that the frailty

Table 1
Characteristics of studies included for a) cross-cohort comparison; and b) studies included for narrative discussion.

Study ID	a) Study First Author, year	Setting: cohort name (if reported)	Number of participants	Mean age at baseline (range)	Women (%)	Baseline period, year(s)	Follow-up period	Number of deficits	Frailty cut- points
1	Thompson et al., 2018	The North West Adelaide Health Study, South Australia	696	73.4 (≥65)	53.1	2004-2006	4.5 years	34	Non-frail (FI≤0.10); Prefrail (0.10<FI≤0.21); Frail (FI>0.21)
2	Ye et al., 2020	China, Shanghai	3988	69.38 (≥60)	56.5	2015	2 years	36	Non-frail (FI≤0.10); Prefrail (0.10<FI≤0.21); Frail (FI>0.21)
3	Liu et al., 2018	Chinese Longitudinal Healthy Longevity Survey, China	11165	82.6 (80; 100)	52.0	2002	3 years	44	Non-frail (FI≤0.10); Prefrail (0.10<FI≤0.21); Frail (FI>0.21)
4	Armstrong et al., 2015a	USA (Oahu, Hawaii): Honolulu-Asia Aging Study	3845	77.9 (≥71)	Men only	1991	Approximately every 3 years	48	Not reported
5	Armstrong et al., 2015b	USA (Oahu, Hawaii): Honolulu-Asia Aging Study	3845	Not reported (72; 93)	Men only	1991	Every 2-3 years over 20 years	NR	Not reported
6	Bartley et al., 2016	USA (Olmsted County, Minnesota): Mayo Clinic Study of Aging	2356	78.8 (70; 89)	49.8	2008	Every 15 months	36	Fit (FI≤0.10); At Risk (0.10<FI≤0.20); Frail (0.21≤FI<0.30); Frailest (FI>0.30)
7	Blodgett et al., 2017	USA: National Health and Nutrition Examination Survey	8888	49.4 (≥20)[a]	51.7	2003-2006	Not reported	68	Frailty scores are categorised incrementally
8	Chamberlain et al., 2016	USA (Olmsted County, Minnesota)	12270	70.5 (60; 89)	55.0	2005	8 years	32	Not reported
9	Fallah et al., 2011	USA (New Haven, Connecticut): Yale Precipitating Events Project	754	78.0 (≥70)	64.0	Not reported	Every 1.5 years	36	Not reported
10	Shi et al., 2020	USA: The National Health and Aging Trends Study	7033	Not reported (≥65)	55.8	2011-2016	Not reported	41	Percentile distribution
11	Brown et al., 2020	USA: Lifestyle Interventions and Independence for Elders Study	1635	79.0 (≥70)	67.2	Not reported	3 years	75	Percentile distribution
12	Mitnitski et al., 2007	Canada: Canadian National Population Health Survey	4330	67.1 (≥55)	58.8	1994-1995	Every 2 years	22	Not reported
13	Mitnitski et al., 2012	Canada: Canadian National Population and Health Survey	4333	68.4 (≥55)	58.8	1994	12 years (every 2 years)	31	Not reported
14	Rockwood et al., 2007	Canada: Canadian Study of Health and Aging	2305	73.4 (69; 109)	53.1	1990-1991	Not reported	70	Non-frail (FI<0.25); Frail (FI ≥ 0.25)
15	Song et al., 2010	Canada: National Population and Health Survey	2740	74.0 (>65)	60.8	1994-1995	10 years	36	Non-frail (FI≤0.08); Pre-frail (0.08<FI<0.25); Frail (FI≥0.25)
16	Zimmer et al., 2021	Canada: Health and Retirement Study	17115	Not reported (≥55)	Not reported	Not reported	Not reported	59	Frailty free (FI≤0.19); Mild frailty (0.19<FI≤0.39); Severe frailty (FI>0.39)
17	Bohn et al. Bonh et al., 2021	Canada: Victoria Longitudinal Study	649	70.6 (53; 95)	66.0	Not reported	Not reported	54	Not reported
18	Mitnitski et al., 2006	Canada: Canadian Study of Health and Aging	5586	Not reported (≥65)	Not reported	1990-1991	Every 5 years	31	Not reported

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Table 1 (*continued*)

Study ID	a) Study First Author, year	Setting: cohort name (if reported)	Number of participants	Mean age at baseline (range)	Women (%)	Baseline period, year(s)	Follow-up period	Number of deficits	Frailty cut- points
19	Hubbard et al., 2009	Canada: The Canadian Study of Health and Aging	9008	Not reported (≥65)	59.5	1991	10 years	40	Not reported
20	Hill et al., 2021	Canada	368798	74.2 (≥55)	46.7	2002-2015	Every year	11 clusters of conditions	Not reported
21	Gale et al., 2017	England: The English Longitudinal Study of Aging	5314	70.0 (50; 75)	54.4	2010-2011	2 years	44	Not reported
22	Gale et al., 2018	England: The English Longitudinal Study of Aging	2817	69.3 (≥60)	56.9	2004-2012	Every 2 years	52	Not reported
23	Niederstrasser et al., 2019	England: The English Longitudinal Study of Aging	8780	66.9 (≥50)	55.02	2004-2005	Every 2 years	Not reported	Frail (FI≥0.25)
24	Rogers and Fancourt, 2020	England: The English Longitudinal Study of Aging	4575	64.7 (≥50)	52.7	2004-2015	10 years	56	Not reported
25	Rogers et al., 2017a	England: The English Longitudinal Study of Aging	8649	64.0 (≥50)	53.2	2002-2003	10 years	56	Non-frail (FI<0.25); Frail (FI≥0.25)
26	Rogers et al., 2017b	England: The English Longitudinal Study of Aging	8722	64.4 (≥50)	54.9	2002-2003	10 years	47	Non-frail (FI ≤0.08); Pre-frail (0.08<FI ≤0.25); Frail (FI>0.25)
27	Stow et al., 2018	England	26298	85.4 (≥75)	55.6	2015	1 year	36	Not reported
28	Hubbard et al., 2010	England: The English Longitudinal Study of Ageing	3055	Not reported (≥65)	55.5	2004	Not clear	58	Not reported
29	Ma et al., 2018	China: Beijing Longitudinal Study of Aging	1810	74.5 (≥60)	51.9	2004	8 years	68	Frail (FI≥0.25)
30	Zheng et al., 2016	China: Beijing Longitudinal Study of Aging	10039	70.5 (≥55)	61.0	2009	1 year	34	Frail (FI≥0.25)
31	(Gu et al., 2009)	China: Chinese Longitudinal Healthy Longevity Survey	13861	Not reported (65; 109)	57.2	2002	3 years	39	Quartile
32	Shi et al., 2011	China: Beijing Longitudinal Study of Aging	3257	Not reported (≥55)	Not reported	1992	Every 2-3 years	35	0.10, 0.20, 0.30, 0.40, 0.5.
33	Woo et al., 2015	China: Beijing Longitudinal Study of Aging II; Hong Kong cohort	11298	Not reported (≥55 Beijing cohort, ≥65 Hong Kong cohort)	57.0	2009 (Beijing cohort); 2001 (Hong Kong cohort)	Every 2-3 years	30 (Beijing cohort), 33 (Hong Kong cohort)	Non-frail (FI<0.25); Frail (FI ≥ 0.25)
34	Hao et al., 2018	China: The Project of Longevity and Aging in Dujiangyan	705	93.6 (90; 108)	67.4	2005	4 years	34	Non-frail (FI<0.21); Frail (FI ≥0.21)
35	Fang et al., 2012	China: The Beijing Longitudinal Study of Aging	3257	Not reported (≥55)	Not reported	1992	8 years	33	0.03, 0.1, 0.20, 0.50
36	Gobbens and Van Der Ploeg, 2021	The Netherlands (Roosendaal)	1154	80.3 (≥75)	56.8	2008	1,2,3,4,5,6 and 7 years	15	Frail (FI≥5)
37	Drubbel et al., 2013	The Netherlands	1679	Median 73 (≥60)	58.8	2008	2 years	36	Tertile
38	Hoogendijk et al., 2017	The Netherlands: The Longitudinal Aging Study Amsterdam	2218	Not reported (55; 85)	Not reported	1995-1996	19 years	32	0.10, 0.20, 0.30, 0.40
39	Hoogendijk et al., 2018	The Netherlands: The Longitudinal Aging Study Amsterdam	1,659	75.7 (≥65)	52.9	1995 -1996	17 years	32	Non-frail (FI<0.25); Frail (FI ≥ 0.25)

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Table 1 (*continued*)

Study ID	a) Study First Author, year	Setting: cohort name (if reported)	Number of participants	Mean age at baseline (range)	Women (%)	Baseline period, year(s)	Follow-up period	Number of deficits	Frailty cut- points
40	Blodgett et al., 2016	Eight European countries: European Male Aging Study	3369	60.2 (40; 79)	Men only	2003	4 years	39	Frailty scores are categorised incrementally
41	Jazbar et al., 2021	Europe: Survey of Health, Ageing and Retirement Survey	25225	73.8 (≥65)	55.5	2013	2 years	30	Frail (FI≥0.25)
42	Romero-Ortuno and Kenny, 2012	Europe: The Survey of Health, Ageing and Retirement in Europe	29905	Not reported (≥50)	54.2	2004	1 year	40	Quartile
43	Romero-Ortuno, 2014	Europe: The Survey of Health, Ageing and Retirement in Europe	29905	Not reported (≥50)	54.2	2004	1 year	40	Quartile
44	Hyde et al., 2016	Australia: Kimberly region	363	60.7 (≥45)	54.5	2004 -2006	7 years	20	Non-frail (FI<0.2); Frail (FI≥0.2)
45	Siejka et al., 2020	Australia (Tasmania): The Tasmanian Study of Cognition and Gait	388	72.0 (65; 80)	44.0	2005-2008	Every 2 years	41	Not reported
46	Souto Barreto et al., 2018	France: Multidomain Alzheimer's Preventive Trial	Control group: 842; Multidomain group: 837	Control: 75.3 (≥70); Multidomain group: 75.3 (≥70)	Control group: 65.0; Multidomain group: 64.3	Not reported	6 months; 1, 2 and 3 years	32	Frail (FI≥0.25)
47	Herr et al., 2015	France: SIPAF[b]	2350	83.3 (≥70)	59.4	2008-2010	Median 2.8 years	43	0.11; 0.17; 0.29
48	Gao et al., 2017	Germany (Saarland): ESTHER[c]	Discovery set: 978; Validation set: 531	Discovery set: 62.1 (50; 75); Validation set: 62.0 (50; 75)	Discovery set: 49.4; Validation set: 61	2000-2002	Not reported	34	Non-frail (FI≤0.20); Pre-frail (0.20<FI<0.45); Frail (FI≥ 0.45)
49	Saum et al., 2014	Germany (Saarland): ESTHER[c]	9886	62.0 (50; 75)	50.0	200-2002	10 years	34	0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45
50	Jung et al., 2014	Korea: Korean Longitudinal Study on Health and Aging	693	75.9 (≥65)	50.8	2005-2006	5 years	Not reported	Pre-frail (0.2≤FI<0.35); Frail (FI≥0.35)
51	Nari et al., 2021	Korea: Korean Longitudinal Study of Aging	2375	Not reported	Not reported	2008	2 years	Not reported	Robust (FI≤1); Pre-frail (1≤FI≤2); Frail (FI ≥2)
52	Hollinghurst et al., 2019	Wales	496000	75.0 (≥65)	55.0	2000-2009	1, 3 and 5 years	36	Fit (efi≤0.12); Mild (0.12<efi≤0.24); Moderate (0.24 <efi ≤0.36); Severely frail (efi>0.36)
53	Kamaruzzaman et al., 2010	Great Britain: The British Women's Heart and Health Study	Not reported	Not reported (60; 79)	100.0	1999-2001	Median 8.2 years	35	Not reported
54	Bartosch et al., 2018	Sweden: Osteoporosis Risk Assessment study	1044	75.2 (≥75)	100.0	1995-1999	5 years and 10 years	13	Varies for each year category
55	Amblas-Novellas et al., 2021	Spain: Patients admitted to the Acute Geriatric Unit	590	86.4 (≥85)	57.5	2015	2 years	25	No frailty (FI≤0.2); Mild frailty (0.2<FI≤0.35); Moderate frailty (0.35<FI≤0.5); Advanced frailty (FI>0.5)
56	Ozmen et al., 2020	Turkey	99	74.0 (≥70)	64.7	2018	10 months	Not reported	Not reported
57	Ohashi et al., 2021	Japan (Agano city): The Kihon Checklist survey	551	67.3 (65; 70)	51.9	2011-2016	5 years	25	Robust (0; 3); Prefrail (4; 7); Frail (≥8)
58	Chen et al., 2021	Taiwan's National Health Insurance Reimbursement Database	100000	Median 73 (≥65)	51.6	2006	Mean 7.58 years	Not reported	Not clear

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Table 1 (*continued*)

Study ID	a) Study First Author, year	Setting: cohort name (if reported)	Number of participants	Mean age at baseline (range)	Women (%)	Baseline period, year(s)	Follow-up period	Number of deficits	Frailty cut- points
59	Borges et al., 2021	Brazil: The Multimorbidity and Mental health Cohort Study in Frailty and Aging	315	Not clear (≥60)	Not clear	Not clear	Not clear	36	Not clear
60	García-González et al., 2009	Mexico: The Mexican Health and Aging Study	4082	73 (65; 105)	52.5	2001	2 years	34	0.07, 0.14, 0.21, 0.35, 0.65
61	Li et al., 2016	Ten countries: Global Longitudinal Study of Osteoporosis in Women 3-Year Hamilton cohort	3985	69.4 (≥55)	100.0	2008-2009	1, 2 and 3 years	34	Frailty scores are categorised incrementally

[a] Analysis is stratified by age categories.
[b] Système HERR, M., ROBINE, J.-M., AEGERTER, P., ARVIEU, J.-J. & ANKRI, J. 2015. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. *Annals of Epidemiology,* 25**,** 674-680.e1. d'Information sur la Perte d'Autonomie Fonctionnelle de la personne âgée.
[c] Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung.

Table 2
Annual transition probabilities.

Thompson et al., 2018	Annual transition			
Frailty status at baseline	Non-frail	Pre-frail	Frail	Death
Non-frail	0.86	0.12	0.01	0.01
Pre-frail	0.06	0.79	0.13	0.01
Frail	0.00	0.03	0.89	0.08
Ye et al., 2020	Annual transition			
Frailty status at baseline	Non-frail	Pre-frail	Frail	Death
Non-frail	0.84	0.13	0.02	0.01
Pre-frail	0.27	0.57	0.15	0.01
Frail	0.03	0.17	0.68	0.12
Liu et al., 2018	Annual transition			
Frailty status at baseline	Non-frail	Pre-frail	Frail	Death
Non-frail	0.62	0.34	0.00	0.04
Pre-frail	0.09	0.70	0.15	0.07
Frail	0.00	0.07	0.65	0.28

increases with age (ID:1,2,5–9,15–17,19–21,23,28–33,35–41,44–47, 49,50,52,53,60), results with respect to gender are inconsistent. Seventeen studies reported that females are more likely to develop frailty (ID:2,15,16,20,21,23,27,30,31,33,35,36,41,47,49, 50,60), whereas one study found frailty worsening in men (ID:1) and another reported that FI score is higher in males than in females (ID:6). Two studies found that frailty, as measured by a FI, is associated with greater risk of death in older women (ID:6,61), whilst other studies reported the opposite – older women tolerated deficits better than men as older men tend to have higher death rates (ID:15,31,32,49,60).

3.5. Association between FI and psychosocial and behavioural factors

Several risk factors associated with progression to higher frailty states are reported in the included studies. These factors include urbanicity (ID:30,31,33,35), smoking (ID:8,19,21,23,48) and/or alcohol consumption (ID:8), obesity (ID:1,23,28), low intensity of physical activity (ID:2,21,23,29,33), low income status (ID:16,21,36,43,47), low level of education (ID:2,6,8,16,23,33,36,43), not married (ID:2,8,33,36), lonely (ID:22,23,39) or living alone (ID:1,2,33), and not having shower facilities at home (ID:2). One study reported that stratification by gender revealed that non-frail women living alone are less likely to transit to a higher frailty state, whereas such association for non-frail men was not confirmed (ID:1). Two studies reported that social isolation did not predict change in frailty index (ID:22,23). The rate of increase in frailty was lower with more frequent engagement in cultural activities (ID:24) and religious activities (ID:31). Among older people smoking and alcohol consumption become less influential factors in frailty progression (ID:8,33,47).

3.6. Association between progression of frailty, physical and mental health

The likelihood of developing frailty increases with the number of chronic conditions (ID:1,30,45,61), multimorbidity (ID:1,33) and/or comorbidity (ID:20), late-life depression (ID:59) and/or taking medication (ID:1,30,33,41).

People with better baseline mobility are more likely to experience improvement in frailty or remain stable, while those with poor baseline mobility are more likely to die (ID:9). One study showed that multidomain interventions that included cognitive training, counselling to effect nutrition and advice on physical activity seem to decrease risk of progression in frailty (ID:46), and another reported that a physical activity intervention is effective among frailest older people (ID:11). Moreover, moderate physical activity reduces progression in frailty among people aged 65 and above, and vigorous physical activity reduces progression in frailty among older people (ID:25).

3.7. FI as a predictor of adverse health outcomes, mortality, and hospital outcomes

The included studies report that a FI is a significant predictor of cognitive decline (ID:4,17,51) or dementia (ID:26), adverse outcomes such as decline in activities of daily living disability or functional decline (ID:10,30,50), falls (ID:10,30,35,61), and death (ID:14,26,30,42,49). Studies that explored association between FI and mortality risk reported that:

a) the frailest people are more likely to die (ID:5,6,12,14,15,20,27, 44,54,56,58,60);
b) an increase in the number of frailty deficits of the FI increases the risk of death (ID:5–7,12,14,18,32,35,38,40,44,49,55,60), and institutionalisation (ID:40,44,53);
c) age is a significant predictor of death among the most people (ID:5,12,15,31,40); and FI score is a predictor of time to death (ID:5);
d) worsening in frailty or remaining in the same frailty state increases the risk of a painful death (ID:3);
e) people aged 90 and over with frailty and cognitive impairment have higher risk of death (ID:34).

The included studies report that a FI is also a significant predictor of hospitalisation (ID:10,30,50,52,53). Frailer people have higher chances to be hospitalised or readmitted to a hospital (ID:20), die in the year following unplanned hospitalisation (ID:20,52,58) or stay longer in hospital (ID:20,52). Healthcare costs after a hospital admission tend to be higher among frailer people (ID:20).

3.8. Predictive ability of FI compared with other tools

Compared to the Schonberg (Schonberg et al., 2009) and Lee (Lee et al., 2006) indices, FI better predicts decline in activities of daily living and falls, but its predictive ability of mortality is comparable to these two prognostic indices (ID:10). When FI is compared to the phenotype measure of frailty, FI predicts adverse outcomes as accurately as phenotype frailty (ID:14), but better predicts mortality, functional decline and hospitalisation when using a weighting factor approach (ID:50). At the same time these two methods (FP and FI) do not share the same risk factors - loneliness is a risk factor for progression in frailty when it is measured with FP, but not a predictor for change in FI (ID:22).

4. Discussion

The results of this systematic review showed that combining evidence from existing literature on frailty operationalised using a research standard frailty model is a challenging task due to dependence of frailty progression on age and inconsistency in how the frailty index is defined and measured across studies. We addressed the latter challenge of synthesising the evidence from those studies that have the same cut points between frailty states. We converted transitions probabilities to annual transition rates to standardise follow-up period and facilitate comparison.

In line with a recently published systematic review that used a phenotypic defined frailty [9], this review showed that worsening in frailty was a common frailty transition. Improvement and stability in frailty status were also possible.

Consistent with the previous literature, where frailty was measured using the frailty phenotype (Kojima et al., 2019; Thompson et al., 2018; Espinoza et al., 2012; Gill et al., 2006; Lee et al., 2014) this review found that frailty tends to increase with time, people who are frail at baseline have greater likelihood to progress in frailty and die, and that age is the main factor that accelerates progression in frailty. Other risk factors for progression in frailty were: having chronic disease, smoking, obesity, low-income or/and low-education level.

The controversial results with respect to association between transition in frailty, survival rates, social status and gender might be due to cohort limitation in the included studies and the male-female health-survival paradox, when compared to men women tend to have a greater chance of survival despite having more health-related issues (Alberts et al., 2014).

This review shows that the FI approach has several advantages and disadvantages stemming from differences in the way the cumulative frailty model has been operationalised in different data sets. First, the FI approach does not require a specific set of health deficits to construct a frailty index. Second, the approach enables usage of routinely collected data extracted from large healthcare databases across the world instead of conducting interviews. Using these large datasets allows for a comprehensive within cohort analysis. Third, a frailty index has better predictive power of adverse health outcomes, hospitalisation, and mortality, and finally FI has more opportunity to observe frailty trajectory. On the other hand, the flexible nature of this approach limits cross-cohort comparison. The inconsistency in cut points used to define frailty indices states prevents comprehensive between cohort analysis.

We could not conduct a comprehensive meta-analysis due to the high level of heterogeneity in the evidence on frailty transitions. We were also unable to conduct subgroup analysis by gender due to limited data reported in the included studies. Heterogeneity in age across cohorts presented a challenge when synthesising evidence across cohorts.

This review is the first to provide synthesised evidence on frailty transition between the stages of frailty and to death among community-dwelling older people, as well as to demonstrate the associations between frailty indices and social and behavioural factors, and the capacity of FI to act as an accurate predictor of adverse outcomes and death. Another strength of the review is the comprehensive methodology including extensive and reproducible search strategy using seven electronic databases. The identified studies were screened with standardised processes and assessed for methodological quality independently by two reviewers.

The review findings contribute to understanding frailty progression in older people living in the community and underscore the role of geriatric medicine in smoothing natural progression of human life to death. The frailty index is proved to be a flexible tool to measure frailty transitions. Moreover, it allows measurement of frailty in many cohorts, for which FI estimates seemed to be similar - older people with frailty are more likely to experience deterioration and, like in the review on phenotypic frailty (Kojima et al., 2019), the reverse is also possible. Hence, FI is a useful tool for a within cohort comparison. The between cohorts' comparison yet is a challenging task. Multidomain lifestyle interventions may help to reduce the risk of becoming frail (Souto Barreto et al., 2018). Therefore, it is important to identify signs of frailty at an earlier stage to help older people with some level of frailty to slow down the progression in frailty and/or delay the incidence (Souto Barreto et al., 2018).

To summarise, measuring frailty using cumulative deficits offers a practical approach with the potential to achieve greater sensitivity to interventions, provided a sufficient range of deficits is included. The definition of frailty states, essentially a categorisation of the frailty index, might be considered with the support of a mapping to a phenotype frailty measure to provide greater consistency between studies.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101789.

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